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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/812,393	03/05/1997	LINDA A. SHERMAN	313332000100	2284

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	08/812,393	SHERMAN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9-10-03 et al.*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9-22-03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The after final amendment filed 7-1-02 was entered upon request for continued prosecution (filed 10-28-02). A non-responsive letter was sent out on 12-30-02 because support for amendments to the claims was not provided. Applicants amended page 4, lines 1-3, pg 4, lines 11-2, Figures 3A-D, 7A-D and 8, and pg 9, Table 1, (1-13-03), and provided support for amendments to the claims (1-16-03). A second non-responsive letter was sent on 4-10-03 because the sequence disk filed on 1-13-03 had errors. Applicants responded by reiterating the amendments to pg 4, lines 1-3, pg 4, lines 11-12 and Fig. to Figures 3A-D, 7A-D and 8 as well as a new amendment to Table 1, in which the amino acid sequence of H12 was changed. A third non-responsive letter was sent on 6-25-03 because the SEQ ID NOs in Table 1 were deleted. Applicants responded on 9-10-03 by requesting withdrawal of the request to amend Table 1. While the last response by applicants is not considered "responsive," the following office action is set forth to expedite prosecution. (The response is non-responsive because amendments cannot be withdrawn. To add the SEQ ID NOs back into the Table and to change the amino acid sequence of H12 back to the original sequence, applicants must replace the pending Table with a corrected Table using the proper format for amending the specification.)

Claims 6-21 were canceled in the after final amendment of 1-16-03 (now entered). Claims 1-5 remain pending and are under consideration in the instant office action. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The sequences on pg 9, Table 1, do not have SEQ ID NO**. Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing." Failure to fully comply with the sequence rules in response to the instant office action will be considered non-responsive.

Please make sure that any amendments to the amino acid sequence of H12 in Table 1 correlates to the amino acid sequence of SEQ ID NO:51 in the pending computer readable format and paper listing.

The amendment filed 1-13-03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: altering the amino acid sequence of H12 from HLYQGOQW to HLYQGCQVV in the amendment filed 1-13-03 and again in the amendment filed 5-9-03 is new matter. Specifically that "O" should have been "C" or that "W" should have been "VV". The sentence cited by applicants as providing support (pg 8, lines 25-27) does not make sense. "eighteen peptides were

synthesized based on the sequence of the human Her-2/neu protein wherein each sequence contained the anchor motif for HLA A2.1, that is, L, I, M, V, A, T at position 2 and position 8/9/10 (Rupert. J. et al. Cell (1993) 74 :929-937)." It is unclear how 6 amino acids fill 4 positions (2, 8, 9 and 10). The sequences in question cannot be found in Rupert. Therefore, it is not readily apparent that pg 8, lines 25-27, or anywhere else in the specification supports such an amendment. Applicant is required to cancel the new matter in the reply to this Office Action.

The blanks on pg 13 were deleted in the amendment filed 7-1-02.

Claim Rejections - 35 USC ' 112

The rejection of claims 1-5 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolating a nucleic acid molecule encoding a TAA-specific mouse TCR comprising: 1) administering a TAA to a transgenic mouse whose genome comprises a nucleic acid sequence encoding HLA-A2 operably linked to a promoter, wherein said mouse functionally expresses HLA-A2 on the surface of an APC and presents the TAA on the surface of the APC in the context of HLA-A2, 2) isolating TAA-specific CTL from the mouse, and 3) isolating a nucleic acid molecule encoding TAA-specific mouse TCR from the TAA-specific CTL, does not reasonably provide enablement for using the method with p53, has been withdrawn because p53 was deleted from claim 1 in the amendment filed 7-1-02.

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the phrase "prepare... ...a nucleic acid sequence encoding at least one of each of the variable regions of the α and β chains" as newly amended is indefinite. The claim fails to set forth the structure of the nucleic acid sequence prepared by stating it comprises a nucleic acid sequence of an α chain TCR and a nucleic acid sequence of a β chain TCR. As written, it appears the claim may encompass a nucleic acid molecule encoding each of the possible α chains and each of the possible β chains.

Claim 1 is indefinite because "said nucleic acid molecules" (line 9) lacks antecedent basis. Only the phrase "nucleic acid molecule" occurs prior to line 9. in addition, the "molecule" in line 1 does not encode anything as in line 9; the molecule in line 1 comprises a sequence encoding at least one variable region.

Claim 1 remains indefinite because the phrase "recovering said HLA restricted CTL, which contain said nucleic acid molecules encoding at least one of each of the variable regions of the α and β chains" is unclear. The claim fails to set forth the structure of the CTL recovered by stating they comprises a nucleic acid sequence of a variable TCR α chain and a nucleic acid sequence of a variable TCR β chain. As written, the language used is confusing because it refers back to "said nucleic acid molecules" which is also unclear (see above). It is also unclear whether the claim

encompasses recovering a CTL having a nucleic acid sequence encoding each of the possible α chains and each of the possible β chains.

Claim 1 is indefinite because it is unclear if both the α and β chains are cloned/amplified in lines 11-12, or if only one or the other is cloned/amplified. In fact, it is unclear that any part of the variable region is cloned/amplified because a non-variable region sequence in the nucleic acid molecule may be cloned/amplified. As written, any portion of the molecule may be cloned or amplified, including non-variable regions sequences. The claim does not clearly set forth that a variable TCR α and β chain are cloned/amplified.

Claim 1 is indefinite because it is unclear if both the α and β chains are recovered in line 13. The phrase "TCR receptor-encoding nucleic acid molecules" lacks antecedent basis. As written, any portion of the molecule may be cloned or amplified, including non-variable regions sequences. Therefore, it is unclear that both the α and β chains would be recovered. The claim does not clearly set forth that a variable TCR α and β chain fusion protein is recovered.

Claim 1 is indefinite because it is unclear to what "fusing the recovered nucleic acid molecules" in lines 14-15 refers. The phrase "the nucleic acid molecule[s]" occurs on line 1, 9, 11 and 13. It is unclear whether the claim is limited to an α chain fused to β chain, or if any two chains recovered in line 13 are fused together are encompassed by the claim. It is unclear whether any variable chain fused together with another nucleic acid sequence is encompassed by the claimed. The claim does not clearly set forth the nucleic acid sequences being fused together.

Claim 1 is indefinite because the metes and bounds of what applicants consider a single chain TCR cannot be determined (line 15). It is unclear if a "single chain TCR" encompasses any β chain by itself or if the phrase is limited to a fusion protein of a TCR α and β variable region.

Claims 4 remains indefinite because the "cloning or amplifying step" in claim 1 does not "comprise" anything, so it cannot "further comprise" anything.

Claim Rejections - 35 USC ' 103

Claims 1-5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Man (1994, J. Immunol., Vol. 153, pages 4458-4467) in view of Cole (April 1995, FASEB Journal, Vol, 9, page A801, abstract 4638) for reasons of record.

Man taught immunizing transgenic mice expressing HLA-A2.1 with $M1_{(58-66)}$ (influenza antigen), isolating CTL from the mice that lyse the M1, amplifying DNA encoding the α and β chain of the M1-specific TCR by PCR (pg 4459, col. 1, "influenza-specific CTL from HLA-A2.1 transgenic mice"; pg 4459, col. 2, "PCR amplification and sequencing of TCR α- and β-chain cDNA). The primers used by Man were mouse α and β TCR-specific primers Vβ8, Vβ5 and Vβ6, which are the primers Vβ8.1, Vβ8.2, Vβ8.3, Vβ5.1 and Vβ6 primers in Fig. 6. The Man did not teach isolating TAA-specific TCR from the mice. However, Cole taught isolating MART-1-specific, HLA-A2 restricted CTL and the α and α chains of TCR recognizing MART-1 from the CTL (see entire abstract). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of isolating TCR genes from transgenic

mice taught by Man to obtain TCR genes specific for the MART-1 antigen. One of ordinary skill would have been motivated to replace the M1 antigen with the MART-1 antigen to obtain MART-1 specific TCR *in vivo*.

Man taught "fusing the recovered nucleic acid molecules together to prepare the isolated nucleic acid molecule" as newly amended because the recovered nucleic acid molecules were fused together with the PBKS- vector. The claim does not require recovering a nucleic acid sequence encoding an α chain and a β chain. Nor does it require fusing a nucleic acid sequence encoding an α chain to a nucleic acid sequence encoding a β chain.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120. The Examiner's number will be changed on January 12th, 2004 to 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER